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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/323,597	06/01/99	AFAR	D 1703-007.US1

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EXAMINER	
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ART UNIT	PAPER NUMBER
1642	10

DATE MAILED: 07/03/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/323,597	AFAR ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 20-31* is/are pending in the application.

4a) Of the above claim(s) *2-5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 20-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

The Election filed May 30, 2000 (Paper No. 9) in response to the Office Action of April 26, 2000 is acknowledged and has been entered. Claims 1-5,20-31 are pending in the application and Claims 2-5 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1, 20–31 are currently under prosecution

Applicant's election with traverse of Group 1, claim 1 in Paper No 9 is acknowledged. The traversal is on the ground(s) that the inventions have not been shown to be independent and the examination of all groups would not impose a serious burden on the examiner. This is not found persuasive. MPEP 802.01 provides that restriction is proper between inventions which are independent or distinct. Here, the inventions of the various groups are distinct for the reasons set forth in Paper No. 7.

As to the question of burden of search, the inventions are classified differently, necessitating different searches in the US Patent shoes. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search. Different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Priority

This application claims priority to three provisional applications- 60/087,596 filed 06/01/98; 60/091,474 filed 06/29/98, and 60/129,521 filed 04/14/99. A review of 60/087,596 revealed an unrelated invention as it was filed by a different applicant. A review of 60/091,474, did not reveal the presently claimed invention as depicted in Figure 1 (SEQ ID NO:2) in the present application. Thus, the examiner has established the priority date according to provisional application No: 60/129,521 filed April 14, 1999.

If applicant disagrees with any rejection set forth in this office action based on examiner's establishment of a priority date of 04/14/99 for the instantly claimed application serial number 09/323597, applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

Specification

The specification on page 1 should be amended to reflect the priority status of the present application, for example:

This application claims benefit to provisional application 60/129,521 filed 04/14/99, now abandoned.

The brief description of Figures 1,2, and 3 are objected to since proper identification of a representative sequence listing (i.e. SEQ ID NOS) is not provided either in the figures or the description. Appropriate correction is required.

The brief description of Figure 3 is further objected to because not all amino acid differences are shown in bold typeface. See for example, amino acid position 160. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 20-25 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims read upon a polypeptide comprising one amino acid residue. See MPEP §1.821 (a).

> Nucleotide and/or amino acid sequences are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. Branched sequences are specifically excluded from this definition. Sequences with fewer than four specifically defined nucleotides or amino acids are specifically excluded from this section.

Claims 1,20-31 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

The disclosed utility for the 20P1F12/TMPRSS2 protein having the amino acid sequence of SEQ ID NO:2 or fragments thereof includes the diagnosis and therapy of prostate and colon cancer (page 4, line 1). However, neither the specification nor any art of record teaches what the 20P1F12/TMPRSS2 is or what it does nor to they do not teach a utility for any of the fragments. In fact, the specification clearly teaches that the function of 20P1F12/TMPRSS2 is unknown

(page 8, line 26). Thus, the asserted utilities for 20P1F12/TMPRSS2, such as the generation of antibodies useful for diagnostic and prognostic assays, imaging methodologies, and therapeutic methods in the management of human cancers such as colon and prostate (page 13, lines 9-22, page 18, line 5) applies to many unrelated polypeptide structure sequences. Therefore, the asserted utilities are not considered "specific" utilities, i.e. they are not specific to 20P1F12/TMPRSS2.

The asserted utility of the 20P1F12/TMPRSS2 is based on the assertion that the 20P1F12/TMPRSS2 (SEQ ID NO:2) has chemical and structural homology to a previously reported human protein, TMPRSS2 which has similarity with members of a serine protease family of proteins. Thus, applicants assert, since proteases are known to be involved in the invasion and metastasis of cancer, the 20P1F12/TMPRSS2 protease could function in the development of metastatic disease (page 8, lines 12-15). However, the specification teaches that the function of TMPRSS2 is also unknown (page 8, line 4) and, as evidenced by Paoloni-Giacobino et al.., the TMPRSS2 protein revealed only 45-55% homology to serine protease family domains. Extending this knowledge to the 20P1F12/TMPRSS2 protein, which differs by 4 amino acids (3 of which are non-conservative substitutions which could effect protease function- page 9, line 20) in the protease domain does not provide substantial credibility that the 20P1F12/TMPRSS2 protein will function like TMPRSS2, or moreover, as a protease. Bowie et al. (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure

from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al. further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al. (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al. (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, with greater than 50% dissimilarity between TMPRSS2 and serine protease family members, the function of SEQ ID NO:2 and fragments thereof could not be predicted nor expected based solely on sequence similarity with TMPRSS2.

Further, the specification teaches that 20P1F12/TMPRSS2 is a prostate specific protease (page 8, line 11). But it is clear that 20P1F12/TMPRSS2 is not prostate specific since it is expressed in other tissues such as colon, pancreas, kidney and lung (page 5, line 24). Moreover,

the specification teaches that equal levels of 20P1F12/TMPRSS2 expression were present in both normal prostate and cancerous prostate (page 5, line 23). Thus, the utility of the 20P1F12/TMPRSS2 protein is clearly not well established. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed polypeptide. Because the claimed invention is not supported by a specific asserted utility for the reasons set forth, credibility cannot be assessed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1,20-31 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a well established for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

In the event that applicant is able to overcome the utility and enablement rejections of above, the following rejection will apply.

Claims 20-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide comprising SEQ ID NO. 2, does not reasonably

provide enablement for polypeptides comprising a fragment of the 20P1F12/TMPRSS2 protein as shown in Fig. 1 (SEQ ID NO:2) wherein a valine is at position 160, or a fragment of the 20P1F12/TMPRSS2 protein wherein an isoleucine is a position 242, or a fragment of the 20P1F12/TMPRSS2 protein wherein glutamic acid is a position 329, or a fragment of the 20P1F12/TMPRSS2 protein wherein lysine is a position 449, or a fragment of the 20P1F12/TMPRSS2 protein wherein an arginine is a position 489, or a fragment of the 20P1F12/TMPRSS2 protein wherein aspartic acid is a position 491.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are drawn to polypeptides comprising a fragment of the 20P1F12/TMPRSS2 protein as shown in Fig. 1 (SEQ ID NO:2) wherein a valine is at position 160, or a fragment of the 20P1F12/TMPRSS2 protein wherein an isoleucine is a position 242, or a fragment of the 20P1F12/TMPRSS2 protein wherein glutamic acid is a position 329, or a fragment of the 20P1F12/TMPRSS2 protein wherein lysine is a position 449, or a fragment of the

20P1F12/TMPRSS2 protein wherein an arginine is a position 489, or a fragment of the 20P1F12/TMPRSS2 protein wherein aspartic acid is a position 491.

This includes a whole universe of polypeptide fragments which comprise any and all amino acids flanking either valine, isoleucine, glutamic acid, lysine, arginine, and or aspartic acid.

The specification teaches (page 7, lines 32-35) that the invention relates to methods and compositions for the diagnosis and therapy of prostate cancer which utilize proteins encoded by the 20P1F12/TMPRSS2 gene and fragments thereof. These include polypeptides and or fragments thereof which exhibit properties of a 20P1F12/TMPRSS2 protein, such as protease activity, protein-protein interactions through specific domains, and binding to substrate molecules in the extracellular milieu (page 8, lines 24-35).

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to any and all polypeptide fragments comprising any amino acid which flanks either valine, isoleucine, glutamic acid, lysine, arginine, and or aspartic acid, and applicant has not enabled all of these types of modified proteins because it has not been shown that these modified proteins are capable of functioning as that which is being disclosed.

The specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative

substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al.. Science, 247:1306-1310, 1990, p. 1306, col.2). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to use any and all polypeptides comprising a fragment of the 20P1F12/TMPRSS2 protein as shown in Fig. 1 (SEQ ID NO:2) wherein a valine is at position 160, or a fragment of the 20P1F12/TMPRSS2 protein wherein an isoleucine is a position 242, or a fragment of the 20P1F12/TMPRSS2 protein wherein glutamic acid is a position 329, or a fragment of the 20P1F12/TMPRSS2 protein wherein lysine is a position 449, or a fragment of the 20P1F12/TMPRSS2 protein wherein an arginine is a position 489, or a fragment of the 20P1F12/TMPRSS2 protein wherein aspartic acid is a position 491.

Therefore, in view of the speculative nature of the invention, the lack of predictability of the prior art, the breadth of the claims and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
June 29, 2000

SUSAN UNGAR, PH.D
PRIMARY EXAMINER